patients, and carvedilol can modulate circulating MMP activity as well as TNF-alpha activity. The inhibition of TNF-alpha activity may directly influence cardiac matrix remodeling in IDC.

11:00 a.m.

844-3 In Vivo Pressure-Volume Analysis of the Cardiac Effects of Chronic Cocaine in Mice

Michael A. Mathier, Jennifer Dawson, Ravi Ramani, Richard P. Shannon, University of Pittsburgh, Pittsburgh, PA, Allegheny General Hospital, Pittsburgh, PA

Background: The relationship between chronic cocaine use and cardiac dysfunction is unclear. Methods: To explore this relationship, mice (C57BL/6) were administered cocaine hydrochloride (30 mg/kg in 0.3cc normal saline) intraperitoneally (COC, n=15) or a similar volume of normal saline (SAL, n=15) daily for 90 days. At the completion of the protocol, survivors were instrumented with a 1.4Fr Millar conductance catheter advanced retrograde into the left ventricle via the right carotid artery. Pressure-volume loops were recorded before and after transient inferior vena caval occlusion at baseline and during IV infusion of dobutamine (5 ug/kg/min). Results: Survival (73% vs. 66%) was similar in the 2 groups. Left ventricular end-diastolic and end-systolic pressures tended to be higher in COC (12+/-4 and 86+/-9 mmHg, respectively) than in SAL (9+/-1 and 80+/-8 mmHg, respectively; p=0.1 for both). Other hemodynamic data are summarized in the table. Ex vivo LV mass (92+/-15 vs. 90+/-8 mg) was similar in the 2 groups. Conclusions: Chronic cocaine administration in mice results in LV dilation, systolic and diastolic dysfunction, and impaired B-adrenergic responsiveness. This may serve as a valuable model for the study of cocaine-associated cardiomyopathy.

	Baseline				Dobutamine				
	HR (bpm)	EDV (ul)	EF (%)	dP/dt/P (sec-1)	Tau (msec)	Ees (mmHg/ul)	EF (%)	dP/dt/P (sec-1)	Ees (mmHg/ul)
SAL (n=6)	567+/-55	18.2+/-3.1	79+/-8	104+/-13	5.9+/-0.4	3.3+/-0.9	90+/-2 #	177+/-15 #	10.9+/-5.1 #
COC (n=6)	507+/-40 *	22.4+/-1.2 *	66+/-4 *	91+/-5 *	7.5+/-1.3 *	2.8+/-0.7	81+/-1 *#	148+/-26 *#	4.2+/-1.6 *

*, p<0.05 vs. SAL; #, p<0.05 vs. baseline. EDV, LV end-diastolic volume; Ees, end-systolic elastance. Values are mean +/- SD.

11:15 a.m.

844-4 Prevalence of Left Ventricular Thrombus in Dilated Cardiomyopathy: The WATCH Trial

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The prevalence of left ventricular thrombus in patients with dilated cardiomyopathy has been estimated at 29-36% in relatively small studies, and is thought to contribute to systemic embolization. **Methods**: We evaluated the prevalence of LV thrombus on 2D echocardiography in the WATCH trial, a multicenter prospective clinical trial of warfarin and antiplatelet agents in dilated cardiomyopathy. Echos were performed prospectively in 1343 patients with NYHA class II-IV CHF and EF≤35% who were in sinus rhythm (age 63 ± 11 years, EF 29 ± 8%, LV end-diastolic volume 194 ±71ml). Patients with recent (<3 mos) myocardial infarction were excluded. **Results**: LV apical mural thrombus was noted in 28 patients (2.1%), and rated as probable or definite in 22, and suspected in 6. The presence of LV thrombus was associated with younger age (59 ± 10 vs 62 ± 11 years, p=. 029), lower EF (24 ± 6 vs 29 ± 8%, p=. 001), higher regional wall motion score (2.2 ± .33 vs 1.91 ± .39, p = .00001) higher velocity of early diastolic filling (85 ± 22 vs 77 ± 28 cm/sec, p=. 0001), longer deceleration time (272 ± 158 msec vs 235 ± 116 msec, p < .0001), greater left ventricular diastolic dimension (6.9 ± .9 vs 6.3 ± .8 cm, p = .05), and greater left atrial area (26 ± 7 vs 21 ± 6 cm^2, p< .00001). The presence of LV thrombus was not related to race, gender, the duration of CHF, prior myocardial infarction, coronary revascularization, or angina, diastolic function pattern, or RV systolic pressure. **Conclusions**: The prevalence of left ventricular thrombus in chronic dilated cardiomyopathy is lower than that previously reported, possibly due to case selection and to improved echocardiographic techniques which lessen near-field artifact. However, the presence of left ventricular thrombus is associated with greater LV cavity size, as well as worse parameters of systolic and diastolic LV function.

11:30 a.m.

844-5 Correlation of Increased Release of Cardiac MMP-1 in Patients With Dilated Cardiomyopathy With Left Ventricular-Diameter

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Background: Interstitial collagen is essential for left ventricular integrity. It has been reported that matrix-metalloproteinases (MMPs) are altered in hearts with dilated cardiomyopathy (DCM). The aim of this study was to test circulating peripheral venous, coronary venous and aortic serum markers of collagen metabolism in DCM. **Methods and Results:** Patients with DCM (n=19; age 44±4 yrs., NYHA class > II, EF <45%, LVEDD >2.9cm/m2) and control subjects with normal LV size and exclusion of myocarditis or coronary artery disease (n=18; age 47±4 yrs.; NYHA class I-III, EF >45%, LVEDD <2.9cm/m2) were investigated. Aortic, peripherhal and coronary venous levels of matrix-metalloproteinase-1 (MMP-1), its inhibitor, tissue inhibitor of metalloproteinase (TIMP-1), were measured using enzyme-linked immunoabsorbent assays. Serum concentrations (aortic, peripherhal and coronary venous) of type I collagen carboxyterminal telopeptide (ICTP; marker of collagen degradation) and the carboxyterminal propeptide of type I procollagen (PICP; marker of collagen synthesis) were determined by radioimmunoassay. Peripheral venous MMP-1 and ICTP serum concentrations were significantly increased in the DCM group (5.03±0.79 ng/ml vs. 2.49±0.95 ng/ml; p=0.02 and 8.05±1.50 ng/ml vs. 4.02±0.71 ng/ml; p< 0.001) as well as the free TIMP-1 concentration (210.59±18.61 ng/ml vs. 137.54±12.78 ng/ml; p= 0.005). PICP was slightly increased in DCM. The coronary venous-aortic difference (coronary sinus minus aorta) of the MMP-1 level was greater in the DCM group (1.58±0.49 vs. -0.59±0.24 ng/ml; p<0.001). The difference correlated with the coronary venous-aortic difference of ICTP (r=0.532; p=0.04). The ICTP- and MMP-difference showed a correlation with LVEDD (r=-0.647; p=0.009 and r=0.526; p=0.04, respectively). **Conclusion:** These findings reveal an increased release of myocardial MMP-1 in DCM. Type I collagen degradation is augmented in DCM. Thus, the increased release of myocardial MMP-1 could be a valuable marker for collagen degradation and LV dilation in DCM.

11:45 a.m.

844-6 A Common Mitochondrial DNA Variant Associated With Left Ventricular Hypertrophy in Type 2 Diabetes Mellitus

Yukihiko Momiyama, Michiko Furutani, Yoshihiko Suzuki, Shin-ichirou Imamura, Kazuhiro Hosokawa, Yoshihito Atsumi, Kempei Matsuoka, Mitsuru Kimura, Fumitaka Ohsuzu, Rumiko Matsuoka, National Defense Medical College, Saitama, Japan, Tokyo Women's Medical University, Tokyo, Japan

Background: DM was reported to be associated with a mitochondrial (mt) DNA mutation at 3243 and variants at 1310, 1438, 3290, 3316, 3394, 12026, 15927 and 16189. Among these mtDNA abnormalities, those at 3243, 3316, 15927 and 16189 were also reported to cause cardiomyopathy. LV hypertrophy (LVH) is common in DM. Some mtDNA abnormalities may play a role in the development of LVH in DM.
Methods: We performed genetic analysis in 33 DM patients (pts) with echocardiographic LVH (wall thickness >12 mm), 79 DM pts without LVH and 100 non-DM controls. After DNA was extracted from blood, a heteroplasmic mutation at 3243 was examined by RFLP analysis using electrophoresis on polyacrylamide gel after ApaI digestion. The 6 mtDNA genes ($tRNA^{LEU}$, $tRNA^{THR}$, 12SrRNA, ND-1, ND-4 and Control), in which the 8 homoplasmic variants described above are present, were analyzed by DNA sequencing.
Results: DM pts with LVH were more hypertensive and obese than those without LVH. Among the reported mtDNA variants, higher prevalence of the 16189 variant was found in DM pts with LVH vs those without LVH and controls (55% vs 23% and 22%, P<0.005) (Table). DNA sequencing also showed that variants at 709 and 16217 were more common in DM pts with LVH than those without LVH (36% and 21% vs 15% and 5%, P<0.025). However, multivariate analysis revealed that the 16189 variant was an independent factor for LVH (OR=5.6, 95%CI 2.0-15.4, P<0.002), but variants at 709 or 16217 were not.
Conclusion: A common mtDNA variant at 16189 was found to be associated with LVH in DM pts.

Prevalence of mtDNA Variants in the 3 Groups

mtDNA variants	1310	1438	3290	3394	12026	15927	16189
DM pts with LVH (n=33)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	1 (3%)	1 (3%)	**18 (55%)***
DM pts without LVH (n=79)	0 (0%)	0 (0%)	1 (1%)	5 (6%)	1 (1 %)	0 (0%)	18 (23%)
Non-DM controls (n=100)	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (3%)	3 (3%)	22 (22%)

P<0.005 vs DM without LVH and controls.
No pt had 3243 mutation or 3316 variant.